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CHOATE, HALL & STEWART LLP
TWO INTERNATIONAL PLACE
BOSTON, MA 02110

EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
12/27/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@choate.com
jhess@choate.com

Office Action Summary	Application No.	Applicant(s)	
	10/775,678	FIGURA ET AL.	
	Examiner	Art Unit	
	DAVID J. STEADMAN	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *124-152* is/are pending in the application.

5a) Of the above claim(s) *138-140 and 150-152* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *124-137 and 141-149* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 124-152 are pending in the application.

Applicant's amendment to the claims, filed on 11/11/11, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

Applicant's remarks filed on 11/11/11 in response to the non-final rejection mailed on 5/13/11 have been fully considered. All previous rejections and objections are withdrawn solely in view of the instant amendment to cancel all previously pending claims. All rejections and objections set forth below are necessitated by the instant claim amendment.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

Claims 138-140 and 150-152 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 124-137 and 141-149 are being examined on the merits with claims 135 and 147 being examined only to the extent the claims read on the elected subject matter, *i.e.,* Iduronate 2-Sulfatase.

Claim Objection

Claim 127 is objected to in the recitation of "endogenous FGE expressed by a heterologous promoter" and in the interest of improving claim form, it is suggested that the noted phrase be amended to recite, *e.g.,* "endogenous FGE, wherein expression of the endogenous FGE is under the control of a heterologous promoter".

Claims 128, 130, 145, and 146 are objected to in the recitation of "exogenous" and in the interest of improving claim form, it is suggested that the term "exogenous" be replaced with, *e.g.,* "heterologous".

Claim Rejections - 35 USC § 112, Second Paragraph

Claims 124-137 and 141-149 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 124 (claims 125-129 and 131-137 dependent therefrom), 130, 141 (claims 142-144 and 146-149 dependent therefrom), and 145 are indefinite in the recitation of "over-expressed" with respect to Formylglycine Generating Enzyme or sulfatase. The examiner can find no definition of "over-expressed" in the specification and the term "over-expressed" is unclear absent a statement defining to what the expression level is being compared. The term "over-expressed" is a relative term and there appears to be nothing in the specification or prior art of record to indicate that one of ordinary skill in the art could have ascertained the level of expression that is intended

to be "over-expressed". It is suggested that applicant clarify the meaning of the noted term. See MPEP 2173.05(b).

Claim 127 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 127 is indefinite in the recitation of "the over-expressed FGE is an endogenous FGE expressed by a heterologous promoter upstream of the endogenous FGE gene" because it is unclear as to whether or not the sulfatase-producing cell requires a heterologous promoter upstream of the FGE gene. In this case, the recitation of "expressed by a heterologous promoter upstream of the endogenous FGE gene" in the noted phrase can be interpreted in at least two different ways: 1) as the process of a product-by-process limitation, which requires only an endogenous FGE, but is not required to be expressed by a heterologous promoter upstream of the endogenous FGE gene (see MPEP 2113) or 2) requiring the presence of a heterologous promoter upstream of an FGE gene in the sulfatase-producing cell. In the interest of giving claims their broadest reasonable interpretation, the examiner has interpreted the noted phrase as the process of a product-by-process limitation, which requires only an endogenous FGE, but is not required to be expressed by a heterologous promoter upstream of the endogenous FGE gene.

Claims 128 and 146 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 128 and 146 are indefinite in the recitation of "an over-expressed FGE" or an "over-expressed sulfatase" that is "an exogenous FGE introduced into the cell" or "an exogenous sulfatase introduced into the cell", respectively. The recitation of "over-expressed FGE" and "over-expressed sulfatase" indicates the FGE and sulfatase are produced in the cell. However, the term "exogenous" means "introduced from...outside the organism or system" (see Office action mailed on 12/28/09 at p. 8, paragraph 17) and thus the phrases "an exogenous FGE introduced into the cell" and "an exogenous sulfatase introduced into the cell" indicate the FGE and sulfatase are produced outside of the cell and then "introduced" into the cell, which is inconsistent with FGE and sulfatase being produced in the cell. It is suggested that applicant clarify the meanings of the noted phrases.

Claims 130 and 145 are indefinite in the recitation of "an exogenous sulfatase over-expressed by the cell" or an "an exogenous FGE over-expressed by the cell" because it is unclear as to the intended meaning of the term "exogenous" in the noted phrases. As noted above, the term "exogenous" means "introduced from...outside the organism or system" (see Office action mailed on 12/28/09 at p. 8, paragraph 17) and thus the term "exogenous" phrases "an exogenous FGE introduced into the cell" and "an exogenous sulfatase introduced into the cell" indicate the FGE and sulfatase are

produced outside of the cell and "introduced" into the cell. It is suggested that applicant clarify the meanings of the noted phrases.

Claims 137 and 149 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 137 and 149 recite the limitation "the mammalian cell". There is insufficient antecedent basis for this limitation in the claims.

Claim Rejections - 35 USC § 112, First Paragraph

Claim(s) 124-137 and 141-149 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a sulfatase-producing cell transformed with an expression vector encoding a cysteine-type sulfatase polypeptide and endogenously expressing an FGE polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:2, wherein the FGE polypeptide modifies a catalytic cysteine to a formylglycine of the encoded sulfatase such that the ratio of active sulfatase to total sulfatase produced by the cell is increased up to 100% over the ratio of active sulfatase to total sulfatase produced by the cell in the absence of FGE,

a sulfatase-producing cell transformed with an expression vector encoding an FGE comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:2 and endogenously expressing a cysteine-type sulfatase

polypeptide, wherein the FGE polypeptide modifies a catalytic cysteine to a formylglycine of the cysteine-type sulfatase such that the ratio of active sulfatase to total sulfatase produced by the cell is increased up to 100% over the ratio of active sulfatase to total sulfatase produced by the cell in the absence of FGE, and

a sulfatase-producing cell transformed with an expression vector encoding an FGE comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:2 and transformed with an expression vector encoding a cysteine-type sulfatase polypeptide, wherein the FGE polypeptide modifies a catalytic cysteine to a formylglycine of the encoded cysteine-type sulfatase such that the ratio of active sulfatase to total sulfatase produced by the cell is increased up to 100% over the ratio of active sulfatase to total sulfatase produced by the cell in the absence of FGE,

does not reasonably provide enablement for all sulfatase-producing cells as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, particularly with respect to the cell modification that results in over-expression of sulfatase and/or FGE.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of

one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The nature of the invention: According to the specification, FGE is an enzyme responsible for post-translationally modifying a conserved cysteine residue in eukaryotes, yielding L-C_{α}-formylglycine, in which an aldehyde group replaces the thiomethyl group of the cysteine (p. 1, lines 20-29). The specification goes on to disclose that FGE can be used to enhance the activity of a sulfatase polypeptide (p. 3, lines 15-19).

The breadth of the claims: **Claims 124-137** are drawn to an isolated sulfatase-producing cell wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased, the cell comprising:

(i) a sulfatase, and

(ii) an over-expressed Formylglycine Generating Enzyme (FGE) comprising an amino acid sequence at least 95% identical to amino acids 34-374 of SEQ ID NO:2,

wherein the ratio of the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed Formylglycine Generating Enzyme.

Claims 141-149 are drawn to an isolated sulfatase-producing cell wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased, the cell comprising:

(i) an over-expressed sulfatase, and

(ii) a Formylglycine Generating Enzyme (FGE) comprising an amino acid sequence at least 95% identical to amino acids 34-374 of SEQ ID NO:2,

wherein the ratio of the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed Formylglycine Generating Enzyme.

The recited "sulfatase" is interpreted as encompassing serine and cysteine-type sulfatases.

The modification to the cell to achieve overexpression of FGE and/or sulfatase has been interpreted as encompassing any modification, including altered mRNAs that have enhanced half-life, mutant transcription factors that regulate endogenous expression of sulfatase and/or FGE, modification to the endogenous sulfatase and/or FGE gene promoter to enhance expression, and modification to the endogenous sulfatase and/or FGE polypeptide to reduce degradation.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: At the time of the invention, the references of Fraser et al. (US Patent 7,083,793 B2; cite A of Form PTO-892 mailed on 5/13/11) and Rosen et al. (US Patent 7,368,793 B2; cite B of Form PTO-892 mailed on 5/13/11) each disclosed

polypeptides, SEQ ID NO:5 and 10571, respectively, having amino acid sequences that are at least 95% identical to the amino acid sequence of SEQ ID NO:2 (see Appendices A and B, respectively, of the Office action mailed on 5/13/11 at pp. 18-19). Rosen et al. further discloses overexpressing the polypeptide in a human cell by transfection with an expression vector (column 311, line 2) and it was well-known that a human cell ubiquitously expresses an arylsulfatase (see, *e.g.,* Ferrante et al., *Eur. J. Human Genet.* 10:813-818, 2002). Also, at the time of the invention, methods for enhancing expression of a polypeptide by transformation or transfection with an expression vector or by promoter replacement were well-known in the prior art.

However, the prior art does not appear to provide any guidance or direction for increasing expression of FGE or sulfatase by any methods other than transformation or transfection with an expression vector or by promoter replacement. Also, at the time of the invention, cellular and polypeptide modifications could be highly unpredictable. For example, the amino acid sequence of a polypeptide determines its structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.,* expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is

highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.,* multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail above. Thus, a skilled artisan would recognize the high level of unpredictability associated with altering the amino acid sequence of a polypeptide.

The state of the art provides evidence for the high degree of unpredictability in altering a polypeptide sequence with an expectation that the altered polypeptide will have the desired activity/utility. For example, Dierks et al. (*Cell* 113:435-444, 2003; cited in the IDS filed on 2/28/05) teaches that even single amino acid mutations in the *SUMF1* gene, which encodes human FGE, result in multiple sulfatase deficiency, which is characterized by a catalytically inactive FGE polypeptide (pp. 438-439). See also MPEP 2144.08.II.A.4.(c), which states, "[t]he effect of a conservative substitution on protein function depends on the nature of the substitution and its location in the chain. Although at some locations a conservative substitution may be benign, in some proteins only one amino acid is allowed at a given position. For example, the gain or loss of even one methyl group can destabilize the structure if close packing is required in the interior of domains. James Darnell *et al., Molecular Cell Biology* 51(2d ed. 1990). " Thus, the prior art acknowledges the unpredictability of altering a protein-encoding sequence with an expectation of obtaining a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a polypeptide. Thus, the prior art acknowledges the unpredictability of

altering a protein-encoding sequence with an expectation of obtaining a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a polypeptide.

The amount of direction provided by the inventor and The existence of working examples: The specification discloses the working example of transformation or transfection of a host cell with an expression vector encoding a sulfatase and an expression vector encoding an FGE polypeptide, wherein the FGE polypeptide modifies a catalytic cysteine to a formylglycine of the encoded cysteine-type sulfatase such that the ratio of active sulfatase to total sulfatase produced by the cell is increased up to 100% over the ratio of active sulfatase to total sulfatase produced by the cell in the absence of FGE.

Other than over-expression by transformation or transfection with an expression vector or by promoter replacement, the specification fails to provide any guidance or direction for increasing expression of FGE or sulfatase in a cell.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While overexpressing a desired polypeptide in a cell by transformation or transfection with an expression vector or by promoter replacement was known in the art at the time of the invention, it was not routine in the art at the time of the invention to overexpress a sulfatase and/or FGE by any method encompassed by the claims.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification and the amount of experimentation that

is required, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 124-137 and 141-149 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, particularly with respect to the cell modification that results in over-expression of sulfatase and/or FGE and the correlation between FGE and the type of sulfatase (cysteine- or serine-type) whose activity is increased. This is a written description rejection.

As noted above, **claims 124-137** are drawn to an isolated sulfatase-producing cell wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased, the cell comprising:

(i) a sulfatase, and

(ii) an over-expressed Formylglycine Generating Enzyme (FGE) comprising an amino acid sequence at least 95% identical to amino acids 34-374 of SEQ ID NO:2,

wherein the ratio of the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed Formylglycine Generating Enzyme.

Claims 141-149 are drawn to an isolated sulfatase-producing cell wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased, the cell comprising:

(i) an over-expressed sulfatase, and

(ii) a Formylglycine Generating Enzyme (FGE) comprising an amino acid sequence at least 95% identical to amino acids 34-374 of SEQ ID NO:2,

wherein the ratio of the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed Formylglycine Generating Enzyme.

The recited "sulfatase" is interpreted as encompassing serine and cysteine-type sulfatases.

The modification to the cell to achieve overexpression of FGE and/or sulfatase has been interpreted as encompassing any modification, including altered mRNAs that have enhanced half-life, mutant transcription factors that regulate endogenous expression of sulfatase and/or FGE, modification to the endogenous sulfatase and/or

FGE gene promoter to enhance expression, and modification to the endogenous sulfatase and/or FGE polypeptide to reduce degradation.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Sufficient description to show possession of such a genus "may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. *See University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895.

MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The specification discloses

only the following representative species of the recited genus of sultatase-producing cells:

a sulfatase-producing cell transformed with an expression vector encoding a cysteine-type sulfatase polypeptide and endogenously expressing an FGE polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:2, wherein the FGE polypeptide modifies a catalytic cysteine to a formylglycine of the encoded sulfatase such that the ratio of active sulfatase to total sulfatase produced by the cell is increased up to 100% over the ratio of active sulfatase to total sulfatase produced by the cell in the absence of FGE,

a sulfatase-producing cell transformed with an expression vector encoding an FGE comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:2 and endogenously expressing a cysteine-type sulfatase polypeptide, wherein the FGE polypeptide modifies a catalytic cysteine to a formylglycine of the cysteine-type sulfatase such that the ratio of active sulfatase to total sulfatase produced by the cell is increased up to 100% over the ratio of active sulfatase to total sulfatase produced by the cell in the absence of FGE, and

a sulfatase-producing cell transformed with an expression vector encoding an FGE comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:2 and transformed with an expression vector encoding a cysteine-type sulfatase polypeptide, wherein the FGE polypeptide modifies a catalytic cysteine to a formylglycine of the encoded cysteine-type sulfatase such that the ratio of

active sulfatase to total sulfatase produced by the cell is increased up to 100% over the ratio of active sulfatase to total sulfatase produced by the cell in the absence of FGE.

In this case, the species encompassed by the genus are widely variant, including species of sulfatase-producing cells having any modification(s) that achieve over-expression of sulfatase and/or FGE. Other than transformation or transfection of a host cell with an expression vector or promoter replacement, the specification fails to disclose any other modification(s) that will achieve over-expression of sulfatase and/or FGE. Moreover, other than the relationship between an FGE comprising the amino acid sequence of SEQ ID NO:2 modifying a catalytic cysteine to a formylglycine of a *cysteine-type sulfatase*, the specification fails to disclose modifying a catalytic serine of a serine-type sulfatase by an FGE comprising the amino acid sequence of SEQ ID NO:2.

Given the lack of description of a representative number of peptides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

Claim Rejections - 35 USC § 102/103

Claims 124, 126, 128-129, 131-134, 136, 141, 143, 145, and 148 are rejected under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Fraser et al. (US Patent 7,083,793 B2; cite A of Form PTO-892 mailed on 5/13/11; hereafter "Fraser") as evidenced by Landgrebe et al.

(Gene 316:47-56, 2003; cite W of Form PTO-892 mailed on 5/13/11; hereafter "Landgrebe") and Dierks (*Cell* 113:435-444, 2003; cite CS of the IDS filed on 2/28/05, hereafter "Dierks"). See MPEP 2112.III regarding a rejection under 35 U.S.C. 102/103 and see MPEP 2131.01 regarding a multiple reference rejection under 35 U.S.C. 102.

Claims 124, 126, 128-129, 131-134, and 136 are drawn to an isolated sulfatase-producing cell wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased, the cell comprising:

(i) a sulfatase, and

(ii) an over-expressed Formylglycine Generating Enzyme (FGE) comprising an amino acid sequence at least 95% identical to amino acids 34-374 of SEQ ID NO:2,

wherein the ratio of the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed Formylglycine Generating Enzyme.

Regarding **claim 124**, the reference of Fraser discloses the amino acid sequence of a polypeptide, SEQ ID NO:15, that is at least 95% identical to amino acids 34-374 of SEQ ID NO:2 herein (see Appendix A sequence alignment of the Office action mailed on 5/13/11 at p. 18).

Fraser teaches inserting a polynucleotide encoding the polypeptide into an expression vector and transforming *E. coli* or transfecting a mammalian cell with the expression vector for recombinant protein expression (columns 47-49, particularly column 48, lines 9-21 and column 49, lines 50-51).

Although Fraser does not expressly disclose *E. coli* is a sulfatase producing cell, evidentiary reference Landgrebe teaches *E. coli* carries cysteine-type sulfatase genes (p. 55, column 1, bottom) and is thus considered to be a cysteine-type sulfatase producing cell.

Although Fraser does not expressly disclose a mammalian cell is a sulfatase producing cell, evidentiary reference Dierks teaches sulfatases in eukaryotes are post-translationally modified at cysteine (p. 435, column 1) and thus a mammalian cell is considered to be a cysteine-type sulfatase producing cell.

Regarding the limitations, "wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased" and "wherein the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed Formylglycine Generating Enzyme", although Fraser does not teach an *E. coli* or mammalian cell recombinantly expressing the SEQ ID NO:15 polypeptide increases active sulfatase activity, since the cell of Fraser expresses a cysteine-type sulfatase, this is a necessary characteristic of the cell of Fraser. Since the Office does not have the facilities for examining and comparing applicant's cell with the cell of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the cell of the prior art does not possess the same material structural and functional characteristics of the claimed cell). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594. This meets the recited limitation.

Regarding **claim 126**, in view of the recitation of the grammatically indefinite article "an", the phrase "an amino acid sequence of SEQ ID NO:2" is interpreted as any two contiguous amino acids of the amino acid sequence of SEQ ID NO:2. SEQ ID NO:15 of Fraser comprises at least two contiguous amino acids of the amino acid sequence of SEQ ID NO:2 herein (see Appendix A sequence alignment).

Regarding **claim 128**, Fraser discloses the polypeptide of SEQ ID NO:15 is a human polypeptide (column 10, lines 54-56) and when the polypeptide of SEQ ID NO:15 is recombinantly expressed in an *E. coli* host cell is exogenous to *E. coli.*

Regarding **claim 129**, as noted above, in view of evidentiary references Landgrebe and Dierks, *E. coli* and eukaryotes, respectively are considered to be cysteine-type sulfatase producing cells and are considered to endogenously produce cysteine-type sulfatase.

Regarding **claims 131-134**, as noted above, although Fraser does not teach an *E. coli* or mammalian cell recombinantly expressing the SEQ ID NO:15 polypeptide increases active sulfatase activity, since the cell of Fraser expresses a cysteine-type sulfatase, this is a necessary characteristic of the cell of Fraser.

Regarding **claim 136**, as noted above, Fraser discloses the host cell can be a mammalian cell (*e.g.,* column 49, lines 50-51).

Claims 141, 143, 145, and 148 are drawn to an isolated sulfatase-producing cell wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased, the cell comprising:

(i) an over-expressed sulfatase, and

(ii) a Formylglycine Generating Enzyme (FGE) comprising an amino acid sequence at least 95% identical to amino acids 34-374 of SEQ ID NO:2,

wherein the ratio of the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed Formylglycine Generating Enzyme.

Regarding **claim 141**, according to MPEP 2173.06, "...where the degree of uncertainty is not great, and where the claim is subject to more than one interpretation and at least one interpretation would render the claim unpatentable over the prior art, an appropriate course of action would be for the examiner to enter two rejections: (A) a rejection based on indefiniteness under 35 U.S.C. 112, second paragraph; and (B) a rejection over the prior art based on the interpretation of the claims which renders the prior art applicable". As noted above, it is unclear as to the level of expression that is intended as being encompassed by "over-expressed" with respect to sulfatase. Also, the recitation of "over-expressed" does not appear to structurally and/or functionally distinguish the recited sulfatase from that of the prior art.

As noted above, the reference of Fraser discloses the amino acid sequence of a polypeptide, SEQ ID NO:15, that is at least 95% identical to amino acids 34-374 of SEQ ID NO:2 herein (see Appendix A sequence alignment).

Fraser teaches inserting a polynucleotide encoding the polypeptide into an expression vector and transforming *E. coli* or transfecting a mammalian cell with the

expression vector for recombinant protein expression (columns 47-49, particularly column 48, lines 9-21 and column 49, lines 50-51).

Although Fraser does not expressly disclose an *E. coli* cell or a mammalian cell as a sulfatase producing cell, evidentiary reference Landgrebe teaches *E. coli* carries cysteine-type sulfatase genes (p. 55, column 1, bottom) and evidentiary reference Dierks teaches sulfatases in eukaryotes are post-translationally modified at cysteine (p. 435, column 1). Also, neither the claims nor the specification requires a particular level of expression of sulfatase to be considered an "over-expressed sulfatase". As such, the *E. coli* cell and the mammalian cell of Fraser are each considered to be cells comprising an over-expressed cysteine-type sulfatase.

Regarding the limitations, "wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased" and "wherein the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed Formylglycine Generating Enzyme", although Fraser does not teach an *E. coli* or mammalian cell recombinantly expressing the SEQ ID NO:15 polypeptide increases active sulfatase activity, since the cell of Fraser expresses a cysteine-type sulfatase, this is a necessary characteristic of the cell of Fraser. Since the Office does not have the facilities for examining and comparing applicant's cell with the cell of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the cell of the prior art does not possess the same material structural and functional characteristics of the claimed

cell). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594. This meets the recited limitation.

Regarding **claim 143**, as noted above, in view of the recitation of the grammatically indefinite article "an", the phrase "an amino acid sequence of SEQ ID NO:2" is interpreted as any two contiguous amino acids of the amino acid sequence of SEQ ID NO:2. SEQ ID NO:15 of Fraser comprises at least two contiguous amino acids of the amino acid sequence of SEQ ID NO:2 herein (see Appendix A sequence alignment).

Regarding **claim 145**, as noted above, Fraser discloses the polypeptide of SEQ ID NO:15 is a human polypeptide (column 10, lines 54-56) and when the polypeptide of SEQ ID NO:15 is recombinantly expressed in an *E. coli* host cell, the polypeptide is exogenous to *E. coli.*

Regarding **claim 148**, as noted above, Fraser discloses the host cell can be a mammalian cell (*e.g.,* column 49, lines 50-51).

Claims 124-129, 131-137, 141-145 and 147-149 are rejected under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Rosen et al. (US Patent 7,368,793 B2; cite B of Form PTO-892 mailed on 5/13/11; hereafter "Rosen") as evidenced by Landgrebe et al. (Gene 316:47-56, 2003; cite W of Form PTO-892 mailed on 5/13/11; hereafter "Landgrebe"), Dierks (*Cell* 113:435-444, 2003; cite CS of the IDS filed on 2/28/05, hereafter "Dierks"), and Ferrante et al. (*Eur. J. Human Genet.* 10:813-818, 2002; hereafter "Ferrante"). See MPEP 2112.III regarding a

rejection under 35 U.S.C. 102/103 and see MPEP 2131.01 regarding a multiple reference rejection under 35 U.S.C. 102.

Claims 124-129 and 131-137 are drawn to an isolated sulfatase-producing cell wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased, the cell comprising:

(i) a sulfatase, and

(ii) an over-expressed Formylglycine Generating Enzyme (FGE) comprising an amino acid sequence at least 95% identical to amino acids 34-374 of SEQ ID NO:2,

wherein the ratio of the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed Formylglycine Generating Enzyme.

Regarding **claim 124**, the reference of Rosen discloses the amino acid sequence of a polypeptide, SEQ ID NO:10571, that is at least 100% identical to SEQ ID NO:2 herein (see Appendix B sequence alignment of the Office action mailed on 5/13/11 at p. 19).

Rosen teaches inserting a polynucleotide encoding the polypeptide into an expression vector and transforming *E. coli* or transfecting an animal cell with the expression vector for recombinant protein expression (columns 309-310).

Although Rosen does not expressly disclose *E. coli* is a sulfatase producing cell, evidentiary reference Landgrebe teaches *E. coli* carries cysteine-type sulfatase genes

(p. 55, column 1, bottom) and is thus considered to be a cysteine-type sulfatase producing cell.

Although Rosen does not expressly disclose an animal cell is a sulfatase producing cell, evidentiary reference Dierks teaches sulfatases in eukaryotes are post-translationally modified at cysteine (p. 435, column 1) and thus an animal cell is considered to be a cysteine-type sulfatase producing cell.

Regarding the limitations, "wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased" and "wherein the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed Formylglycine Generating Enzyme", although Rosen does not teach an *E. coli* or animal cell recombinantly expressing the SEQ ID NO:10571 polypeptide increases active sulfatase activity, since the cell of Rosen expresses a cysteine-type sulfatase, this is a necessary characteristic of the cell of Rosen. Since the Office does not have the facilities for examining and comparing applicant's cell with the cell of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the cell of the prior art does not possess the same material structural and functional characteristics of the claimed cell). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594. This meets the recited limitation.

Regarding **claims 125-126**, as noted above, the amino acid sequence of the polypeptide of Rosen is 100% identical to SEQ ID NO:2 herein.

Regarding **claim 127**, Rosen discloses the polypeptide is a human polypeptide (column 19, line 7) and can be expressed in a human cell (column 311, line 2) and the human polypeptide of Rosen is considered to be "endogenous" when produced in a human cell. Rosen further discloses expression of the polypeptide using a vector construct with an operably associated heterologous promoter polynucleotide (paragraph bridging columns 310-311).

Regarding **claim 128**, Rosen discloses the polypeptide is a human polypeptide (column 19, line 7) and when the polypeptide of Rosen is recombinantly expressed in an *E. coli* host cell, the polypeptide is considered to be "exogenous" to *E. coli*.

Regarding **claim 129**, as noted above, in view of evidentiary references Landgrebe and Dierks, *E. coli* and eukaryotes, respectively, are considered to be cysteine-type sulfatase producing cells and are considered to endogenously produce cysteine-type sulfatase.

Regarding **claims 131-134**, as noted above, although Rosen does not teach an *E. coli* or animal cell recombinantly expressing the SEQ ID NO:10571 polypeptide increases active sulfatase activity, since the cell of Rosen expresses a cysteine-type sulfatase, this is a necessary characteristic of the cell of Rosen.

Regarding **claim 135**, as noted above, Rosen discloses the host cell can be a human host cell (column 311, line 2) and evidentiary reference Ferrante discloses ubiquitous expression of arylsulfatase G in human cells (p. 813, abstract; p. 817, column 1, middle). As such, the cell of Rosen would inherently produce arylsulfatase G.

Regarding **claims 136-137**, Rosen discloses the host cell can be a mammalian or human cell (*e.g.*, column 311, lines 1-2).

Claims 141-145 and 147-149 are drawn to an isolated sulfatase-producing cell wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased, the cell comprising:

(i) an over-expressed sulfatase, and

(ii) a Formylglycine Generating Enzyme (FGE) comprising an amino acid sequence at least 95% identical to amino acids 34-374 of SEQ ID NO:2,

wherein the ratio of the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed Formylglycine Generating Enzyme.

Regarding **claim 141**, according to MPEP 2173.06, "...where the degree of uncertainty is not great, and where the claim is subject to more than one interpretation and at least one interpretation would render the claim unpatentable over the prior art, an appropriate course of action would be for the examiner to enter two rejections: (A) a rejection based on indefiniteness under 35 U.S.C. 112, second paragraph; and (B) a rejection over the prior art based on the interpretation of the claims which renders the prior art applicable". As noted above, it is unclear as to the level of expression that is intended as being encompassed by "over-expressed" with respect to sulfatase. Also, the recitation of "over-expressed" does not appear to structurally and/or functionally distinguish the recited sulfatase from that of the prior art.

As noted above, the reference of Rosen discloses the amino acid sequence of a polypeptide, SEQ ID NO:10571, that is at least 95% identical to amino acids 34-374 of SEQ ID NO:2 herein (see Appendix B sequence alignment of the prior Office action).

Rosen teaches inserting a polynucleotide encoding the polypeptide into an expression vector and transforming *E. coli* or transfecting an animal cell with the expression vector for recombinant protein expression (columns 309-310).

Although Rosen does not expressly disclose an *E. coli* cell or an animal cell as a sulfatase producing cell, evidentiary reference Landgrebe teaches *E. coli* carries cysteine-type sulfatase genes (p. 55, column 1, bottom) and evidentiary reference Dierks teaches sulfatases in eukaryotes are post-translationally modified at cysteine (p. 435, column 1). Also, neither the claims nor the specification requires a particular level of expression of sulfatase to be considered an "over-expressed sulfatase". As such, the *E. coli* cell and the animal cell of Rosen are each considered to be cells comprising an over-expressed cysteine-type sulfatase.

Regarding the limitations, "wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased" and "wherein the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed Formylglycine Generating Enzyme", although Rosen does not teach an *E. coli* or animal cell recombinantly expressing the polypeptide increases active sulfatase activity, since the cell of Rosen expresses a cysteine-type sulfatase, this is a necessary characteristic of the cell of Rosen. Since the Office does not have the facilities for examining and

comparing applicant's cell with the cell of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the cell of the prior art does not possess the same material structural and functional characteristics of the claimed cell). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594. This meets the recited limitation.

Regarding **claims 142-143**, as noted above, as noted above, the amino acid sequence of the polypeptide of Rosen is 100% identical to SEQ ID NO:2 herein.

Regarding **claim 144**, as noted above, Rosen discloses the polypeptide is a human polypeptide (column 19, line 7) and can be expressed in a human cell (column 311, line 2) using a vector construct with an operably associated heterologous promoter polynucleotide (paragraph bridging columns 310-311).

Regarding **claim 145**, as noted above, Rosen discloses the polypeptide is a human polypeptide (column 19, line 7) and when the polypeptide of Rosen is recombinantly expressed in an *E. coli* host cell, the polypeptide is exogenous to *E. coli*.

Regarding **claim 147**, as noted above, Rosen discloses the host cell can be a human host cell (column 311, line 2) and evidentiary reference Ferrante discloses ubiquitous expression of arylsulfatase G in human cells (p. 813, abstract; p. 817, column 1, middle). As such, the cell of Rosen would inherently produce arylsulfatase G.

Regarding **claims 148-149**, as noted above, Rosen discloses the host cell can be a mammalian or human cell (*e.g.,* column 311, lines 1-2).

Claims 124-127, 129-137, 141-144, and 146-149 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Rommerskirch et al. (*Proc. Natl. Acad. Sci. USA,* 89:2561-2565, 1992; cite U of Form PTO-892 mailed on 9/17/07; hereafter "Rommerskirch") as evidenced by Dierks et al. (*Cell* 113:435-444, 2003; cite CS of the IDS filed on 2/28/05; hereafter "Dierks"). See MPEP 2112.III regarding a rejection under 35 U.S.C. 102/103 and see MPEP 2131.01 regarding a multiple reference rejection under 35 U.S.C. 102.

Claims 124-127 and 129-137 are drawn to an isolated sulfatase-producing cell wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased, the cell comprising:

(i) a sulfatase, and

(ii) an over-expressed Formylglycine Generating Enzyme (FGE) comprising an amino acid sequence at least 95% identical to amino acids 34-374 of SEQ ID NO:2,

wherein the ratio of the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed Formylglycine Generating Enzyme.

The claims are interpreted as encompassing the cell of Rommerskirch for reasons set forth below.

Regarding the **claim 124** limitations a cultured sulfatase-producing cell and the cell comprising a sulfatase and **claim 135**, the reference of Rommerskirch teaches a metachromatic leukodystrophy (MLD) fibroblast cell infected with a retroviral gene

transfer vector comprising a herpes simplex virus thymidine kinase promoter and a sulfatase-encoding nucleic acid (p. 2562, column 1 and Figure 2), where the cell produces arylsulfatase A (p. 2563, Table 1).

Regarding the **claim 124** limitation an overexpressed FGE comprising an amino acid sequence at least 95% identical to amino acids 34-374 of SEQ ID NO:2 and **claims 125-126**, the evidentiary reference of Dierks discloses that human FGE (p. 437, Figure 3), which is 100% identical to SEQ ID NO:2 herein, is expressed in human fibroblasts (p. 437, column 2, bottom) and the cell of Rommerskirch is a human fibroblast. Also, the transfectant of Rommerskirch is considered to have an "over-expressed" FGE relative to the disclosed multiple sulfatase deficiency (MSD) fibroblasts, which, as noted by evidentiary reference Dierks, MSD fibroblasts are defective in FGE activity (p. 440, Table 2), *i.e.,* are without FGE.

Regarding the **claim 124** limitation, wherein the ratio of the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed FGE and **claims 131-134**, the MLD fibroblasts recombinantly expressing arylsulfatase A necessarily exhibit an increase in the ratio of active sulfatase to total sulfatase of at least 100% as compared to MSD fibroblasts, where MLD fibroblasts and MSD fibroblasts are the same cell type, *i.e.,* fibroblasts, and evidentiary reference Dierks provides evidence that MSD fibroblasts are defective in FGE activity (p. 440, Table 2), *i.e.,* are without FGE.

Regarding **claim 127**, as noted above, the recitation of "the over-expressed FGE is an endogenous FGE expressed by a heterologous promoter upstream of the endogenous FGE gene" is interpreted as a product-by-process limitation and thus the endogenously produce FGE of the MLD fibroblasts recombinantly expressing arylsulfatase A of Rommerskirch satisfies this limitation.

Regarding **claim 129**, the recitation of "the sulfatase is an endogenous sulfatase expressed by the cell" is interpreted as meaning the sulfatase is produced inside the cell and the arylsulfatase A of the MLD fibroblasts recombinantly expressing arylsulfatase A of Rommerskirch satisfies this limitation.

Regarding **claim 130**, as noted above, the term "exogenous" means "introduced from...outside the organism or system" (see Office action mailed on 12/28/09 at p. 8, paragraph 17) and the recitation of "an exogenous sulfatase over-expressed by the cell" is interpreted as meaning a homologous or heterologous sulfatase that is produced as the result of transformation or transfection with a polynucleotide encoding the sulfatase.

Regarding **claims 136-137**, the MLD fibroblasts recombinantly expressing arylsulfatase A of Rommerskirch are human MLD fibroblasts (paragraph bridging pp. 2562-2563).

Claims 141-144 and 146-149 are drawn to an isolated sulfatase-producing cell wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased, the cell comprising:

(i) an over-expressed sulfatase, and

(ii) a Formylglycine Generating Enzyme (FGE) comprising an amino acid sequence at least 95% identical to amino acids 34-374 of SEQ ID NO:2,

wherein the ratio of the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed Formylglycine Generating Enzyme.

Regarding the **claim 141** limitations a cultured sulfatase-producing cell and the cell comprising an over-expressed sulfatase and **claim 147**, the reference of Rommerskirch teaches a metachromatic leukodystrophy (MLD) fibroblast cell infected with a retroviral gene transfer vector comprising a herpes simplex virus thymidine kinase promoter and a sulfatase-encoding nucleic acid (p. 2562, column 1 and Figure 2), where the cell produces arylsulfatase A (p. 2563, Table 1). According to Rommerskirch, MLD fibroblasts do not normally produce arylsulfatase A because of MLD fibroblasts lack arylsulfatase A mRNA and activity (p. 2563, column 1, middle) and thus the transfectant of Rommerskirch is considered to have an "over-expressed" sulfatase.

Regarding the **claim 141** limitation an overexpressed FGE comprising an amino acid sequence at least 95% identical to amino acids 34-374 of SEQ ID NO:2 and **claims 142-144**, as noted above, the evidentiary reference of Dierks discloses that human FGE (p. 437, Figure 3), which is 100% identical to SEQ ID NO:2 herein, is expressed in human fibroblasts (p. 437, column 2, bottom) and the cell of Rommerskirch is a human fibroblast.

Regarding the **claim 141** limitation, wherein the ratio of the active sulfatase to total sulfatase produced by the cell is increased by at least 5% relative to the ratio of active sulfatase to total sulfatase produced by the cell in the absence of the over-expressed FGE, the MLD fibroblasts recombinantly expressing arylsulfatase A of Rommerskirch necessarily exhibit an increase in the ratio of active sulfatase to total sulfatase of at least 100% as compared to MSD fibroblasts, where MLD fibroblasts and MSD fibroblasts are the same cell type, *i.e.,* fibroblasts, and evidentiary reference Dierks provides evidence that MSD fibroblasts are defective in FGE activity (p. 440, Table 2), *i.e.,* are without FGE.

Regarding **claim 146**, as noted above, the term "exogenous" means "introduced from...outside the organism or system" (see Office action mailed on 12/28/09 at p. 8, paragraph 17) and the recitation of "an exogenous sulfatase introduced into the cell" is interpreted as meaning a homologous or heterologous sulfatase that is produced as the result of transformation or transfection with a polynucleotide encoding the sulfatase.

Regarding **claims 148-149**, the MLD fibroblasts recombinantly expressing arylsulfatase A of Rommerskirch are human MLD fibroblasts (paragraph bridging pp. 2562-2563).

RESPONSE TO REMARKS: At p. 9 of the instant remarks, applicant argues the references of Rosen and Fraser are irrelevant to the claimed invention and the references of Landgrebe and Dierks are not available as prior art.

Applicant's argument is not found persuasive. Regarding the references of Rosen and Fraser, at least for the reasons set forth above, it is the examiner's position that both Rosen and Fraser anticipate, either expressly or inherently, the claimed invention. Regarding the references of Landgrebe and Dierks, these references are not relied upon as prior art, but are cited in accordance with MPEP 2131.01 to show that a characteristic not disclosed in the reference of Rosen or Fraser is inherent.

Beginning at p. 9 of the instant remarks, applicant argues Rommerskirch does not recognize that the absence of FGE in MSD fibroblasts is the defect that affects post-translational modification of sulfatases. Applicant argues that six years of hard work was required to purify FGE. According to applicant, for these reasons it cannot be obvious for one of ordinary skill in the art to purify the FGE protein. Applicant argues that the invention is based on the discovery of FGE as being responsible for post-translationally modifying sulfatases, which was not trivial and is described by two declarations by co-inventor Dierks.

Applicant's argument is not found persuasive. The claims are not directed to a method for identifying FGE as being the factor that modifies a catalytic cysteine of a cysteine-type sulfatase to a formylglycine. Rather, the issue is whether or not the claimed sulfatase-producing cell would have been anticipated at the time of the invention. While it appears that the relationship between FGE and cysteine-type sulfatases, *i.e.,* post-translational modification by FGE of a catalytic cysteine of a cysteine-type sulfatase to a formylglycine, was not recognized at the time of the invention, this does not defeat the anticipation analysis. See MPEP 2112, which states,

"The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103" and see MPEP 2112.I, which states, "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." There is no evidence of record or line of reasoning that supports the position that the claimed sulfatase-producing cell of Fraser, Rosen, or Rommerskirch is distinguished over the prior art of record.

Beginning at p. 10 of the instant remarks, applicant argues the claimed invention solves a long-standing problem with manufacturing sulfatases and has provided unexpected benefits to pharmaceutical manufacturers and patients suffering from sulfatase diseases.

Applicant's argument is not found persuasive. The claims are not directed to a method for manufacturing sulfatases or treating sulfatase diseases. As noted above, the issue is whether or not the claimed sulfatase-producing cell would have been anticipated or obvious at the time of the invention. As further noted above, there is no evidence of record or line of reasoning that supports the position that the claimed sulfatase-producing cell is distinguished over the prior art of record. Here, the reference of Fraser, Rosen, or Rommerskirch anticipates, either expressly or inherently, the claimed invention at least for the reasons set forth above.

Conclusion

Status of the claims:

- Claims 124-152 are pending.
- Claims 138-140 and 150-152 are withdrawn from consideration.
- Claims 124-137 and 141-149 are rejected.
- No claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656